Endometrial Hyperplasia and Carcinoma

Introduction

The last lesson was about the healthy uterus and some problems with uterine structure that cause abnormal uterine bleeding. This lesson focuses on endometrial carcinoma (uterus cancer) and the premalignant lesion endometrial hyperplasia. Many things are known about endometrial carcinoma, but the existing associations and knowledge are incongruent with the conclusions. Specifically, there is definitely an increased risk of endometrial carcinoma among women who had early menarche, late menopause, and nulliparity, but the conclusion is "cumulative estrogen exposure." Wrong. Although those factors do convey an increased risk, and unopposed estrogen can lead to uterine cancer, the conclusion is incorrect, as evidenced by estrogen levels during pregnancy that are tens to thousands of times greater than those outside of pregnancy. The clinical application of "excess estrogen" IS useful, as it provides an increased pretest probability that a woman with postmenopausal bleeding has endometrial carcinoma. But it is egregiously unhelpful when learning the mechanism by which cancer is caused. We will bridge the gap and provide you with an understanding of both.

This lesson is on structural causes of abnormal uterine bleeding that are malignant or premalignant. This is the M in the PALM-COINE mnemonic. There is a heaping whop of endometrial hyperplasia and endometrial carcinoma, with a sprinkle of serous carcinoma of the uterus (we will explain the nomenclature in its section) and endometriosis to close the lesson out.

Endometrial Cancer Is Not Caused by Estrogen Exposure, but by Endometrial Proliferation Exposure

Here is the current dogma. **Endometrial hyperplasia** is a chronic condition that is premalignant on the way to endometrial carcinoma, and both are associated with "**cumulative estrogen exposure**." The conditions that increase a woman's exposure to estrogen are **early menarche, late menopause**, and **nulliparity** (never carried a pregnancy to delivery), as well as **obesity** (peripheral conversion of androgens to estrogen), **estrogen hormone replacement therapy** (exogenous estrogen after menopause to ease hot flashes or "maintain youthfulness"), anovulatory cycles especially caused by **polycystic ovarian syndrome**, and medications such as **tamoxifen** (which is a selective estrogen receptor modulator we will go through in detail in the Breast island, as it treats breast cancer but causes endometrial cancer). More estrogen, more cancer.

You know that sound? The one from the game show "Family Feud." Think Steve Harvey era. When the family member gives an answer that isn't one that was given by the 100 people surveyed? *"We asked 100 endometrial cancers. The top six answers are on the board. We asked them to name the thing that would most likely cause them to become endometrial cancer. And you said, 'cumulative estrogen exposure.'"* ERRRRRRRRGGGGGGHHHHHHHHH and a big ol' red X.

Here is the current dogma taught to you by OnlineMedEd. Precancer, cancer, malignancy, whatever you call it, is the result of **one stem cell** that accumulates sufficient mutations to enable unregulated proliferation, becomes immune to lymphocytes that would induce apoptosis, becomes immortal (ignores telomere length), and to become malignant, gains the ability to invade through the basement membrane. **Accumulation of mutations** results in cancer. Throughout this course, outside of ionizing radiation from unnecessary CT, radiation therapy for another cancer, or an inheritable defect in DNA mismatch repair, we've taught you that healthy cells go bad due to **increased proliferation**. Estrogen is linked to proliferation, but it's also linked to pregnancy.

Endometrial proliferation, NOT "cumulative estrogen exposure," causes the stem cells of the stratum basale of the endometrium to acquire sufficient mutations to turn cancerous.

Early menarche, late menopause, and nulliparity DO increase the risk of malignant transformation. This is because all of those conditions result in **more proliferative cycles** of the uterine endometrium, not more estrogen. Obesity, polycystic ovary syndrome (PCOS), estrogen hormone replacement therapy, and SERMs like tamoxifen DO increase the risk of malignant transformation. That is because of **more proliferation per cycle** of the uterine endometrium, not more estrogen. By the way, it isn't just pregnancy that provides protection; it's bringing a pregnancy to a term birth—the only way to prevent nine cycles (up to 25 depending on how long mom breastfeeds) is to have a gestating fetus with a placenta or a suckling baby that **prevents ovarian cycles**.

Number of Proliferations and Degree of Proliferation Each Cycle

Let's just take a gander at what estrogen levels look like, comparing not-pregnant follicular ovarian cycle estrogen to pregnant, placenta-making estrogen levels.

Estrogen levels are highest during pregnancy. If cumulative estrogen exposure were the risk factor, there would be more endometrial carcinoma in women who have had children, and the incidence rate would increase with each child. But that's not the case: having children is protective against endometrial carcinoma. Why? Because if the uterine endometrium is busy feeding the growing fetus rather than proliferating for nine cycles' worth of time, there's no opportunity for the accumulation of mutations. It **is not cumulative estrogen**, but rather the **cumulative estrogen-driven proliferation of the uterus**. Without ovarian cycles driving uterine cycles, there is no risk of mutation accumulation.

It comes down to the **number of proliferations** (early menarche, late menopause, and nulliparity) and the **degree of proliferation** of each cycle (obesity, estrogen receptor modulators, and estrogen replacement therapy).

Number of proliferations. Let's look at the number of proliferations. The **more uterine cycles**, the **more proliferating** the stratum basale does, and the more opportunity it has to accumulate mutations. If a woman starts having menstrual cycles earlier than average or stops later than average, she experiences more cycles because her reproductive years span a longer period. Lifelong nulliparity means the cycles continued uninterrupted for the entire duration. Each pregnancy prevents endometrial proliferation for a minimum of 9 months, which is usually nine cycles. Something **entirely negates** early menses, late menopause, and nulliparity as risk factors. Know what it is? **Combined hormonal contraception.** Why? Because with combined hormonal contraception (estrogen and **progesterone**), there ain't no uterine cycles. And without them uterine cycles, there ain't no opportunity to accumulate mutations, because proliferation is the prerequisite for mutation accumulation. Said practically, most women have light spotting as menses or the complete elimination of menses altogether while on combined hormonal contraception. **Progesterone is protective** against uterine cancer. So, you can stop calling combined hormonal contraception "contraception" and start calling it "get pregnant when you choose, and also prevent uterine (and ovarian) cancer." We are making a big deal out of this because, in women who never bear children, it is NOT the choice not to bear children that causes cancer of the uterus, but the absence of progesterone-based contraception that increases the risk of getting it. Of course, getting pregnant numerous times also decreases the risk of uterine and ovarian cancer, but that is less practical for young women or those who have more choice over when and if they enter motherhood.

Proliferation per cycle. Other conditions that aren't so obvious are those that don't increase the *number of proliferations* but increase the amount of *proliferating* in each cycle. These are the conditions that increase estrogen exposure—**obesity** (peripheral conversion of androgens into estrogen), **PCOS** (because anovulation prevents the release of progestin), the old-age-reducing **estrogen hormone replacement therapy** (with estrogen alone, which is not done anymore because it increases endometrial cancer, negated by adding progesterone), and even some estrogen receptor stimulators used to treat breast cancer, such as **tamoxifen** (a SERM we will discuss later in the Breast island).

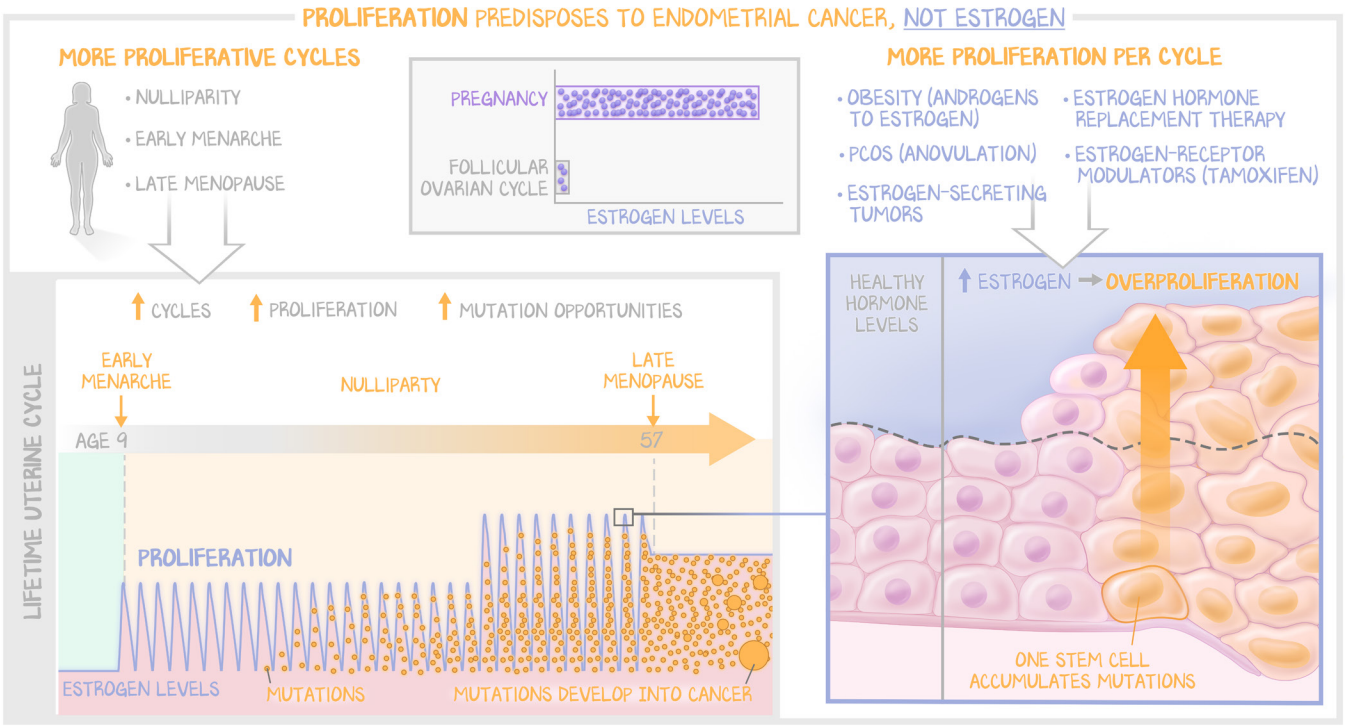

Figure 3.1: Proliferation, Not Estrogen, Predisposes to Cancer
"Cumulative estrogen exposure" conveniently encompasses all of the risk factors for developing endometrial cancer. It is also erroneous. Exposure to estrogen is highest during pregnancy. Estradiol levels approach a thousandfold those of the nonpregnant state. But early menarche, late menopause, and nulliparity do increase the risk of cancer. That is because they all afford more opportunities for proliferation—more uterine cycles. In states of chronically (and pathologically) elevated estrogen (e.g., obesity, anovulatory cycles such as in PCOS, exogenous estrogen administration, tamoxifen), there is more proliferation at each opportunity. Proliferation begets mutations in the stem cells of the stratum basale. The accumulation of mutations leads to cancer. The genes that are mutated first are those that enable estrogen-independent proliferation, which begets even more mutations, even after menopause. According to the stem cell theory of cancer, only one stem cell needs to escape detection by the immune system to cause cancer.

Endometrial Hyperplasia

Endometrial hyperplasia should be considered a premalignant lesion that will progress to endometrial carcinoma. Both the classic-type endometrial carcinoma and endometrial hyperplasia occur in postmenopausal women, presenting as **postmenopausal bleeding**. Postmenopausal vaginal bleeding is cancer until proven otherwise, just as postmenopausal iron deficiency anemia is colon cancer until proven otherwise. Postmenopausal bleeding is more often related to a condition that isn't cancer—such as vaginal atrophy (see Female Reproduction #6: *Reproductive Endocrinology*)—but is serious enough for cancer to be considered with each case. Endometrial hyperplasia and endometrial carcinoma are caused by the accumulation of mutations as a result of increased proliferation. ~~Estrogen is the proliferation signal, so having an increased cumulative estrogen exposure increases risk.~~ **Unopposed estrogen without progesterone** increases the number of cycles (proliferation) and the degree of proliferation in each cycle.

Endometrioid endometrial carcinoma (Type 1, endometrioid, and classic are synonyms, and the "endometrioid" is usually dropped) is the cancer phenotype that demonstrates an overproduction of the surface epithelium of the endometrium. Endometrioid means **simple columbar epithelium that invaginates on itself to form glands** but **without** a matching stromal proliferation. Just as with many other cancers you've learned from us, the precancers and cancers that demonstrates the phenotype of endometrial hyperplasia then endometrial carcinoma have a spectrum of common mutations and a well-understood pattern. when simple columnar epithelial cells accumulate mutations in the RAS-

PI3K arm of the RET receptor. Endometrial hyperplasia, with and without atypia, demonstrates a **loss of function of the *PTEN* gene**, which encodes the protein **PTEN**, which normally **inhibits** the **PI3 kinase** arm of that pathway. We encountered these genetics in Endocrine (see Endocrine: Thyroid #3: *The Unhealthy Thyroid: Structural Disorders*), so we won't re-explore the pathway. We'll also go deeper into those genes next, in endometrial carcinoma. The point is, endometrial hyperplasia demonstrates early the genetic mutations present in endometrial carcinoma, AND endometrial carcinoma tends to show more accumulation of mutations in the same RET pathway.

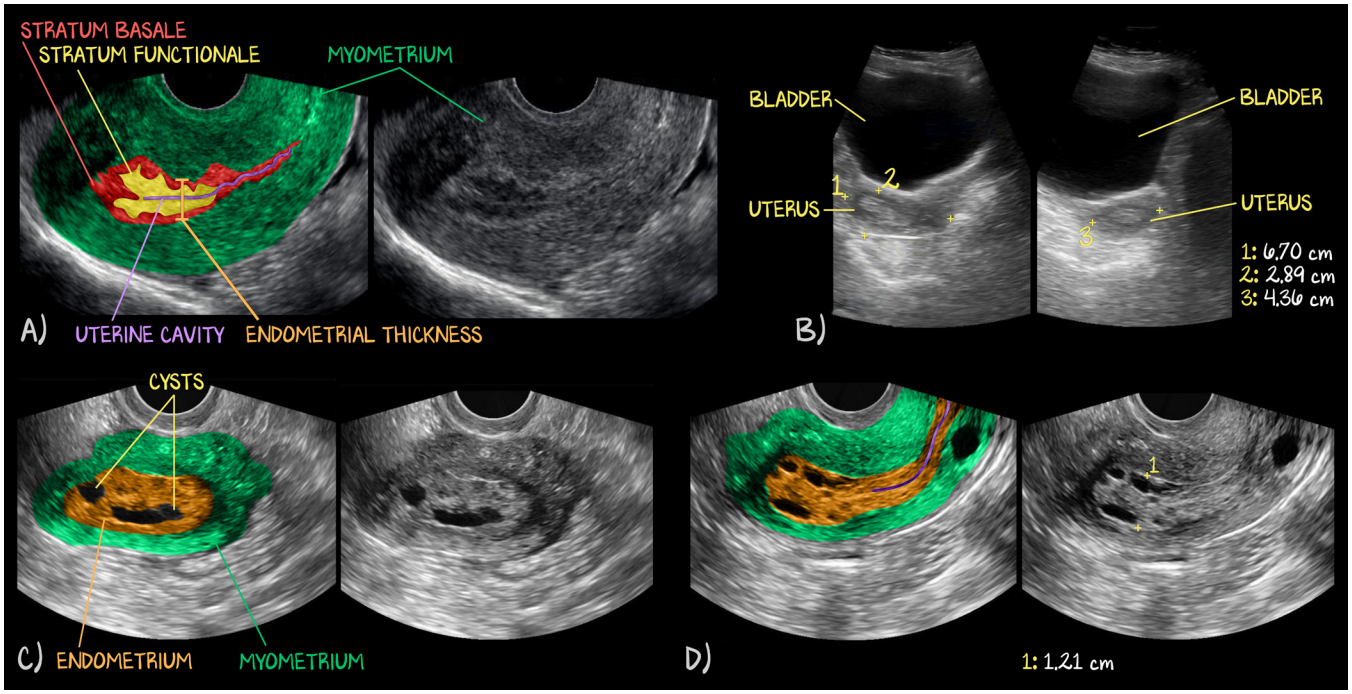

Figure 3.2: Sonographic Endometrial Hyperplasia
(a) Normal uterine ultrasound captured during the secretory phase of the ovarian cycle (so this is the largest the endometrium should be) demonstrating a thick myometrium surrounding a small endometrium. The uterine cavity is barely detectable, and the stratum functionale is the most robust near the fundus, tapering toward the cervix. At the cervix, the myometrium occupies nearly the entire diameter. At the fundus, there is almost no endometrium and the diameter nearly entirely myometrium (b) Transabdominal ultrasound identifying the uterus behind the bladder. The fluid-filled bladder appears black, and the uterus is seen behind it. (c) Transverse transvaginal ultrasound and (d) longitudinal transvaginal ultrasound showing a (slightly) enlarged endometrium. Endometrial hyperplasia may also be accompanied by cysts, as shown in these images. The larger the endometrium and the larger the cysts, the farther the progression toward uterine cancer.

When the stromal cells overproliferated, we got a non-premalignant uterine polyp, when the myometrium overproliferated, we got leiomyomas (fibroids), and when there was overproliferation of the simple columnar epithelium that invaginated on itself to form glands and stroma came with it within the myometrium, we got adenomyosis. **NONE** of those conditions express similar genetics to those seen in endometrial hyperplasia of endometrial carcinoma.

LEIOMYOMA	UTERINE POLYP	ADENOMYOSIS	ENDOMETRIAL HYPERPLASIA
Smooth muscle pushing on endometrium and perimetrium	Stromal proliferation without epithelial proliferation	Simple columnar epithelium that invaginates onto itself **with** stromal proliferation	Simple columnar epithelium that invaginates onto itself **without** stromal proliferation

This next sentence is hyperspecific to the pathology. When a **stem cell** of the simple columnar epithelium that invaginates onto itself to form glands accumulates a specific proliferation mutation—loss of PTEN—we get the proliferation of that stem cell into endometrial hyperplasia. Because there isn't a proliferation signal (estrogen from the ovary), but the cancer stem cell proliferates without regulation, the stem cells of the stroma do not proliferate at the same rate as the cells of the cancerous simple columnar epithelium that invaginates on itself to form glands. This means that when biopsied, the **endometrium is enlarged**, but because the gland-forming epithelium is proliferating in the endometrium (not in the myometrium like adenomyosis), and the stromal cells are not proliferating in the endometrium, there will be far more glands than stroma when compared to normal proliferative endometrium. That is communicated by an **increased gland-to-stroma ratio**. There will be more and taller invaginations of the columnar epithelium, and they will not be accompanied by proliferation of the stroma like that seen in the proliferative phase. That means the glands will be crowded, close to one another. The worse the gland:stroma ratio there is, the more dysplastic changes there usually are. A well-differentiated endometrial hyperplasia with a small increase in the endometrium's thickness and a near normal gland to stromal ratio will progress to poorly-differentiation endometrial carcinoma with dysplasia, very thick endometrium with nearly only glands and no stroma, which evidence of invasion.

Because endometrial hyperplasia is precancer and most commonly occurs in postmenopausal women (past the point of fertility, no longer in need of a uterus), the treatment is surgical—**removal of the uterus** (hysterectomy). Obtaining a biopsy of endometrial hyperplasia is usually done through a dilation and curettage – removing the endometrium. In women who are diagnosed this way with early stage disease, hysterectomy is not required, though still recommended.

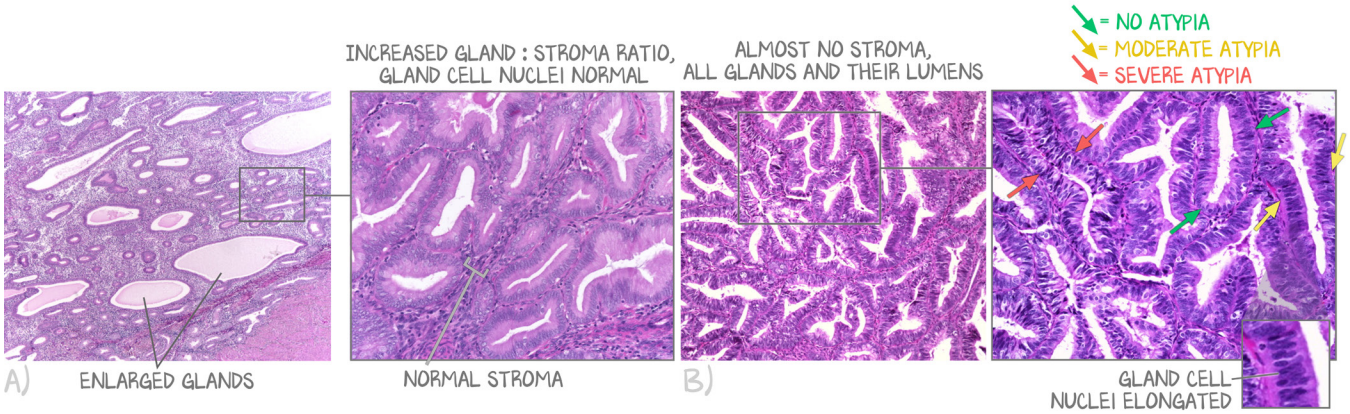

Figure 3.3: Histology of Endometrial Hyperplasia
Endometrial hyperplasia is defined as endometrial proliferation with an increased gland:stroma ratio (from 2:1 to 3:1). (a) Histology showing the proliferation of dilated endometrial glands with no or minimal outpouchings. This is an example of simple hyperplasia without atypia. In the magnified image, the cells' nuclei appear similar to each other and are aligned along the basement membrane, and their apices are oriented toward the lumen. (b) These endometrial glands are highly irregular in size and shape and show frequent outpouchings. The stroma is barely visible between the glands (because there are so many glands). In the magnified image, the atypia is characterized by the enlarged round nuclei, seeming loss of polarity, and amorphous nuclear and cellular shapes. Compare the cells indicated by the yellow arrows (severe atypia) to those denoted by green arrows (nearly normal), then those by orange arrows (between yellow and green).

Endometrial Carcinoma Is Endometrial Hyperplasia with More Mutations

Because we've already addressed the risks of proliferation and estrogen exposure, discussed how progesterone is protective, and introduced *PTEN* genetics, we need not revisit them here. Endometrial carcinoma has no screening tool and has the same presentation as endometrial hyperplasia—postmenopausal vaginal bleeding. The work-up is the same—ultrasound, biopsy. The treatment is the

same unless it has spread—removal of the uterus (hysterectomy). The greater the gland to stroma ratio, the more nuclear pleomorphism, nuclear atypia, asnd nucleus to cytoplasm ratio, the worse the disease.

Endometrioid endometrial carcinoma is the cancer associated with Lynch syndrome, part of the hereditary nonpolyposis colorectal cancer syndromes that involve the microsatellite instability pathway and the loss of DNA repair genes in colon cancer (see Gastrointestinal: Digestion and Absorption: Start to Finish #12: *Neoplasia of the Large Intestine*). Thus, because HNPCC involves microsatellite instability (DNA-mismatch repair genes) and endometrial hyperplasia involves the *PTEN* gene and its associated second-messenger system, we can deduce that the progression to malignant transformation is likely to involve the PI3 kinase arm of the RET receptor and DNA-mismatch repair genetics. For the PI3 kinase arm, most endometrial carcinomas that are already malignant demonstrate multiple mutations. **Loss of function of the *PTEN* gene** (most common, seen in endometrial hyperplasia), gain of function of the **KRAS gene**, and gain of function of the *PIK3CA* gene (which encodes **PI3 kinase**) are readily seen. In addition, and likely parallel to the accumulation of these mutations, is the silencing (via hypermethylation) of the DNA-mismatch repair genes, such as ***MLH1***. This tolerance of mutations, coupled with multiple proliferation signals, leads to the eventual accumulation of ***TP53*** mutations. As is the case in most cancers, loss of p53 is the genetic hallmark that portends invasion and full malignant transformation.

So, although the sequence isn't as clean as the adenoma-carcinoma sequence, there is definitely a gain of proliferation (PI3 kinase arm), tolerance of mutations (*MLH1*), and the eventual terminal signal (*TP53*). The most common type of endometrial carcinoma is **endometrioid carcinoma**. There are also mucinous carcinomas and below, we will characterize serous carcinoma. That fact—endometrioid, serous, and mucinous subtypes—will become useful when we discuss ovarian cancers.

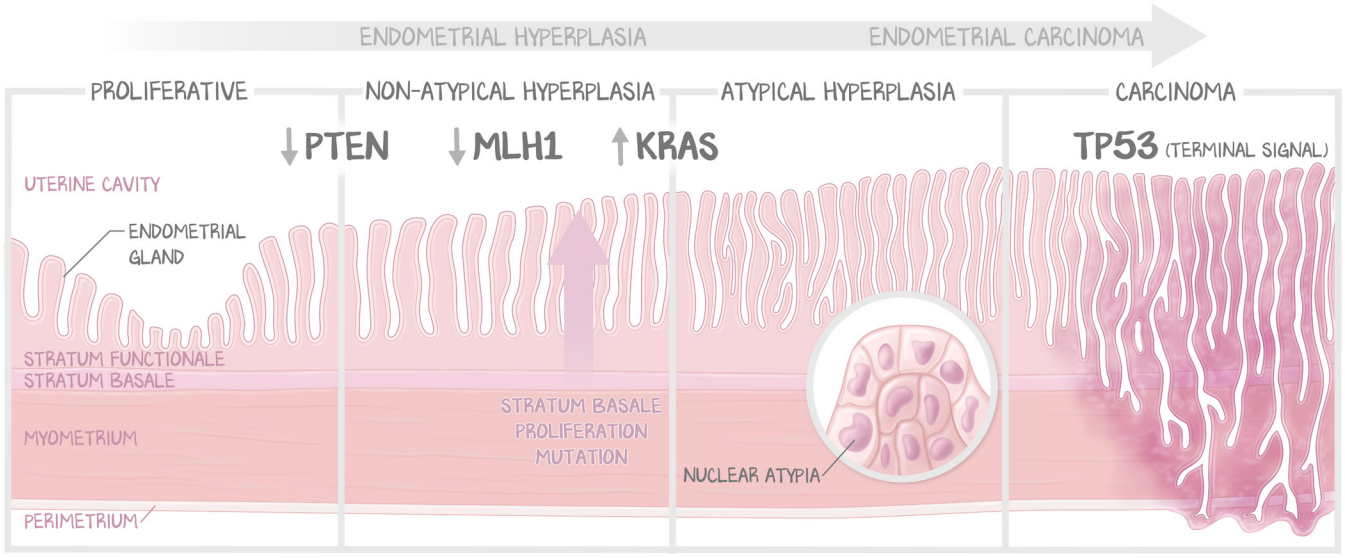

Figure 3.4: The Genetic Path to Endometrial Hyperplasia and Carcinoma

The tumor is of the stratum basale, and proliferation will result in an even higher gland-to-stroma ratio than is seen in endometrial hyperplasia. Spread generally occurs by myometrial invasion followed by **direct extension** to adjacent structures/organs. Invasion of the broad ligaments may create a palpable mass. **Dissemination to the regional lymph nodes** eventually occurs, and in the late stages, the tumor may metastasize to the lungs, liver, bones, and other organs. Because dissemination occurs very late, the **stages are not the ones you would expect**.

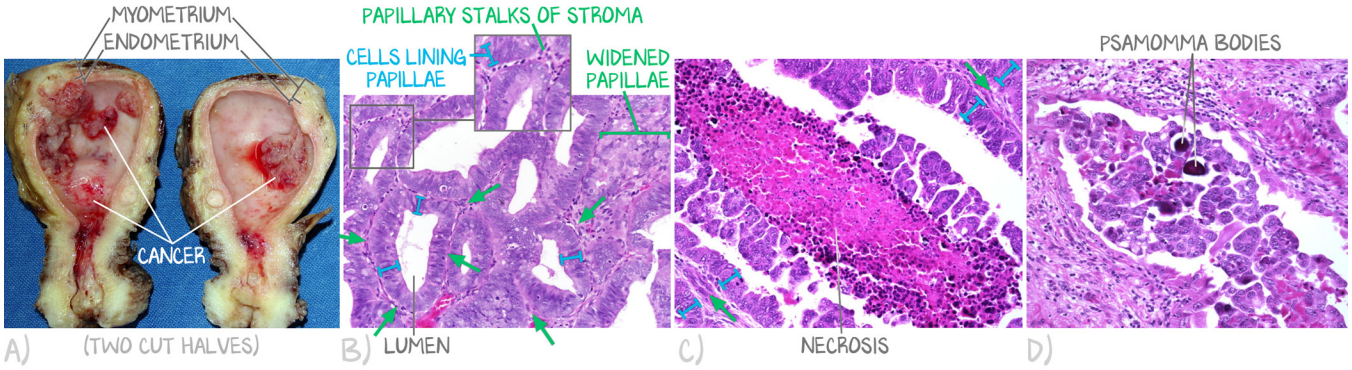

Figure 3.5: Histology of Endometrial Hyperplasia and Carcinoma
(a) Gross specimen of endometrial carcinoma in a bisected uterus demonstrating cancer within the uterine cavity that extends into the cervix. (b) Moderate-magnification light microscopy demonstrating the papillary component—small bands of stroma with cells on either side—indicative of the classic form of endometrial carcinoma (c) High-magnification light microscopy showing two papillae with cancerous cells (upper right and lower left edges) and a papilla with necrosis (across the center of the image). (d) Although uncommon, the dark masses amongst the cells are calcifications called psammoma bodies.

Stage 1 carcinoma is **confined to the body** of the uterus. This is tricky because there is no epithelium invading through a basement membrane—there isn't one between the endometrium and myometrium. Instead, what takes the surrogate role of the basement membrane in most tissues is the "confines of the uterus." This means the cancer can exit the uterus through the uterine tubes, perimetrium, or cervix. The path of least resistance is out through the cervical os. As long as it is within the endometrium, myometrium, and uterine cavity, it is stage 1. **Stage 2** carcinoma involves the **body and cervix**—still confined by the myometrium but now protruding from the uterine cavity through the cervical os into the vagina. Stages 3 and 4 involve the cancer getting out of the uterus. **Stage 3** carcinoma is found outside the uterus but still contained within the pelvis under the peritoneal cavity. **Stage 4** carcinoma is found outside the pelvis or invading any nearby organ (bladder or rectum).

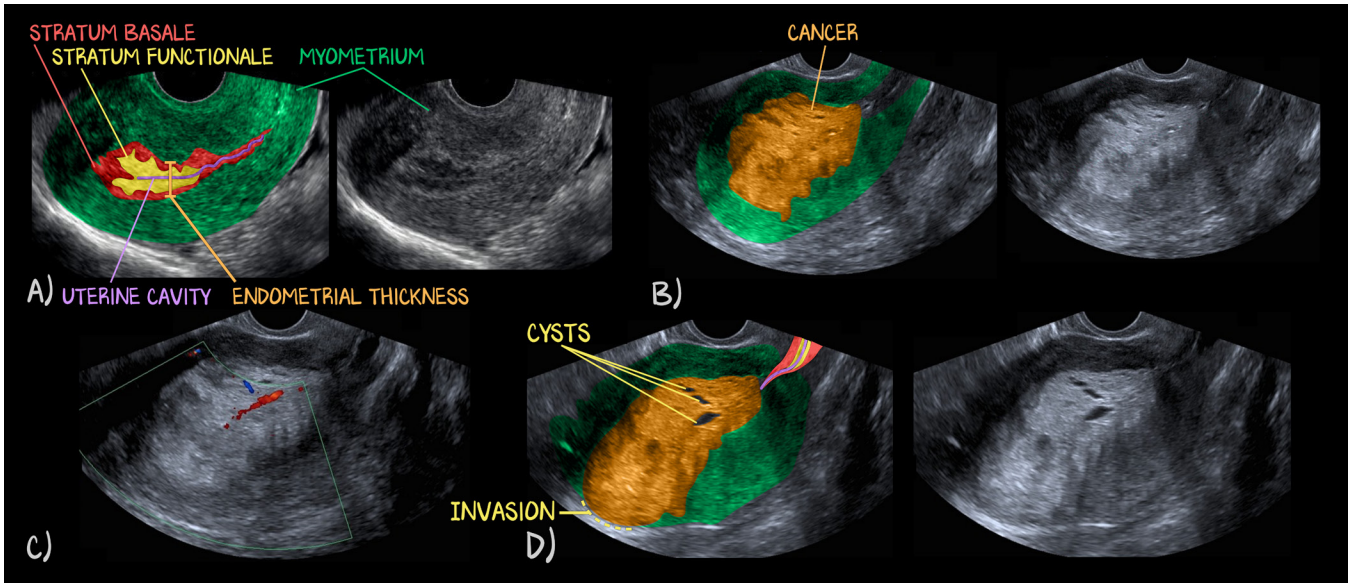

Figure 3.6: Radiographic Endometrial Carcinoma
(a) The normal transvaginal ultrasound from Figure 3.2, for reference. (b) Ultrasound of endometrial cancer demonstrating an inversion of the myometrium: endometrium ratio—the hyperechoic (whiter) endometrium occupies most of the uterus, which is expanded by the cancer's mass. (c) Doppler ultrasound demonstrating increased vascularity (red and blue) indicative of malignancy. (d) Endometrial cancer invading the wall of the uterus. More advanced imaging is required to confirm the staging, and a biopsy is needed to confirm the diagnosis, but this was a case of endometrial carcinoma.

Do not learn any treatment regimens—chemotherapy, surgery, radiation, etc.—for this cancer at this level. You are responsible for the genetic mechanisms, "cumulative estrogen exposure" risk factors, and evaluation of a patient with a vaginal ultrasound/physical exam. So ends the tale of endometrial hyperplasia and endometrial carcinoma, and now we turn to the fascinating topic of endometriosis.

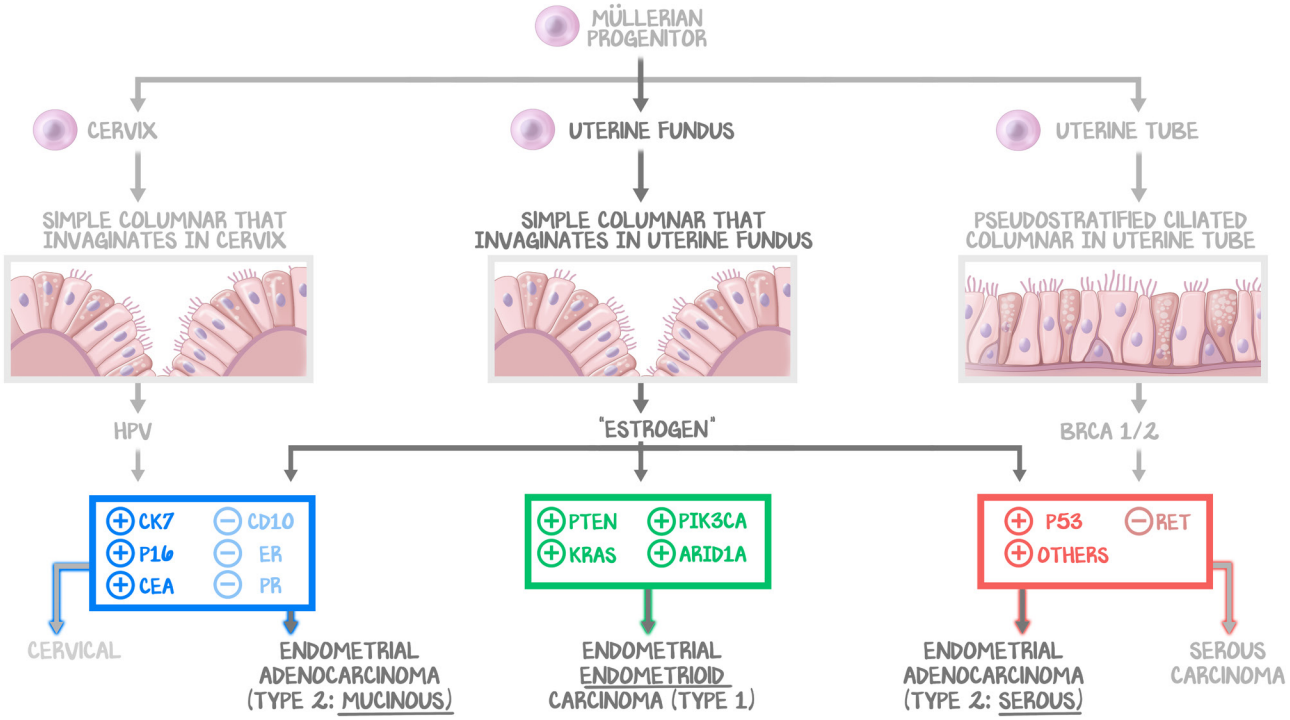

Figure 3.7: Genetics of Endometrial Carcinomas
Early in embryogenesis, a stem cell, a common Müllerian progenitor, produces the stem cells of the Müllerian epithelia. That common progenitor divides and differentiates daughter cells to become the stem cells of the epithelium of the endocervix—simple columnar epithelium that invaginates upon itself and secretes a mucinous fluid. That common progenitor also divides and differentiates daughter cells to become the stem cells of the epithelium of the endometrium, the epithelium of the fundus and corpus—simple columnar epithelium that invaginates upon itself to form glands that do not secrete fluid (only glycoproteins for the placenta). That common progenitor also divides and differentiates daughter cells to become the stem cells of the epithelium of the uterine tube—pseudostratified columnar epithelium that secretes a serous fluid. Cancer results from the accumulation of mutations and subsequent dedifferentiation of a stem cell. Dedifferentiation of stem cells in the uterine tube, uterus, or endocervix sends them back toward the phenotype of their common Müllerian progenitor, enabling them to express a different phenotype than normal, but only one that the common Müllerian progenitor knows how to make. The phenotype is determined by the mutations. Uterine tube cancer is rare. Adenocarcinoma of the endocervix is considered cervical cancer (it is obviously a Müllerian Malignancy and not a cervical cancer, but that is how medical science has categorized it). The endometrium of the corpus and fundus can become a cancer that behaves like the endometrium, the most common endometrial cancer phenotype, type 1 endometrial carcinoma, caused by mutations in PTEN, KRAS, PIK3CA. Endometrial cancer that behaves like adenocarcinoma of the endocervix is type 2 mucinous endometrial carcinoma, which exhibits different mutations than type 1 endometrial carcinoma. If TP53 is mutated early in the disease process, then the phenotype expressed by the cancer is similar to the phenotype of the uterine tube, type 2 endometrial carcinoma.

Honorable Mention: Endometrial Carcinoma Type 2

If endometrial cancer acquires a mutation in *TP53* first rather than last, it will develop into **serous endometrial carcinoma** or a **mucinous endometrial carcinoma**. These cancers have a higher incidence in African-American women, tend to be found later in life (age 65–75), and occur in atrophic uteri. They have a propensity to grow quickly and **seed the peritoneum** early in the disease. These are rare, are outside the illness script for endometrial hyperplasia (including no association with the genetics or exposure to proliferation and estrogen), and have a generally dismal prognosis. Because endometrial

carcinoma is now the most common gynecological cancer (since the advent of PAP tests and HPV vaccines has so significantly reduced cervical cancer), and serous/mucinous carcinomas account for 15% of endometrial carcinoma (and nearly all of the fatalities), we wanted to include them. But we also want you to separate serous/mucinous carcinomas from endometrial carcinoma (don't learn them as type 1 and type 2). Learn them as serous and mucinous carcinomas of the uterus and endometrial carcinoma.

There are three endometrial carcinomas based on the epithelium they express—endometrioid, serous, and mucinous. We want you to remember this when we get to epithelial ovarian cancers.

Endometriosis

This section is what you have to memorize. The section after this one, if you choose to read further, we use what we've taught you so far to deduce the most likely etiology and debunk the current popular belief. Because the mechanism isn't understood, no one should ask you to know it. Instead, the task becomes recognizing the illness script, knowing how to work up infertility, and what to do when you find endometriosis on exploratory laparotomy.

Endometriosis is the presence of **ectopic** and **totally normal endometrium**—most often in the pelvis, sometimes in the abdomen, and rarely in the chest. The ectopic endometrial tissue is called an **endometrioma**.

Endometriosis **is hormone-responsive, normal endometrium** found outside the uterus. It is most often found on the ovary or the lining of the peritoneal cavity. Because of the repeated hemorrhaging and the shape of the ovary, when there is endometriosis in the ovary, it has gotten the name **chocolate cyst**. The dark color is because of the bleeding. The bleeding of endometriosis takes on that color wherever it is found, though it does not appear cyst-like when not within the ovary. There will be growth during the proliferative phase, secretion during the secretory phase, and **bleeding** during the menstrual phase. The bleeding causes **pain** (usually during menses, called dysmenorrhea) and can cause **infertility**. In almost half of all cases of infertility in women, the cause is endometriosis. Abnormal Müllerian duct fusion (anatomic uterine causes) is also responsible for almost half. Because it is estrogen-responsive, the patient is **asymptomatic until menarche** and **improves after menopause**. The diagnosis cannot be anticipated by physical exam (which is normal or sometimes associated with a retroverted uterus), laboratory tests (because the tissue is normal but ectopic), or imaging. The diagnosis is found after an exhaustive search for other diagnoses, usually in the pursuit of fertility. Eventually, an **exploratory laparotomy** (go into the abdomen to take a look around because all else has failed) will reveal the presence of the lesion. Resection or ablation is curative, and the lesions do not recur (aligning with the ectopic Müllerian duct theory). If infertility is not an issue, the pain can often be controlled with over-the-counter analgesics, such as NSAIDs, and **hormonal contraception** can eliminate symptoms.

Nowadays, with the abundance of oral contraceptive pills and intrauterine contraceptive devices, with the recommendation from ACOG that all girls 13 and older receive some form of hormonal contraception, the incidence of endometriosis is decreasing or at least being delayed. Hormonal contraception often results in the absence of menses because of the progesterone. Without ovulatory cycles, the endometrium doesn't proliferate and slough off, ova are not released, and there is no estrogen signal. This prevents the proliferation and sloughing of endometriosis as well. Therefore, hormonal contraception may mask endometriosis by suppressing symptoms until the woman comes off contraception. For the reasons listed above, hormonal contraception is also protective against endometrial carcinoma (limiting the effects of cumulative estrogen and the number of proliferations of the stratum basale) and epithelial ovarian cancers (for reasons we have not yet told you about).

Endometriosis Mechanism

The remainder of this note set includes information you do not have to know for licensure. If you are with us to get by, to prepare for a licensure examination alone, you need not read further. Below is the unknown, as yet unestablished by medical science. But it enables us to use what we've taught you, combined with what medical science does know, to work through this problem logically. This isn't us tooting our own horn, because we don't know what the answer is, either. But OME Basic Sciences, unlike any resource that came before, links multiple modules to comprehend one disease that, so far, medical science has found incomprehensible. We don't want you to think we know what is when we don't. We do want you to realize that, because you can follow along with the subsequent discussion, you have achieved an understanding that most healthcare providers have never achieved. Memorize and regurgitate? Not here. Use the knowledge and comprehension you know to be true to evaluate the potential etiologies of a condition that has "remained a mystery for decades."

Gynecologists don't know what the mesothelium, intraembryonic coelom, or primary sex cords are because they don't ever have to deal with them while performing exploratory surgery to remove an endometrioma, curing a woman of menstrual pain and potentially infertility. Embryologists don't know what an endometrium is or what a menstrual cycle is because menarche happens anywhere from 8 to 15 years after birth, long after an embryologist's job is done (birth). You know both.

The current leading theory (which we entirely reject) is that endometriosis is caused by **retrograde flow**—the movement of menstrual tissue through the uterine tubes, traveling to the ovaries and seeding the peritoneum. This is an attractive explanation because the ovaries and the peritoneal lining of the pelvic floor are where endometriosis is most commonly found. But that explanation doesn't work because endometriosis can be found in the chest—above the diaphragm and far away from the uterus and ovaries, which are under the peritoneal cavity. That explanation also doesn't work because the tissue expelled during menses is **ischemic and already necrotic** and lacks the cells necessary to form an epithelium—the stem cells of the endometrium are in the stratum basale, not the stratum functionale that is sloughed off. Finally, even if the stratum basale were to become dislodged, the contraction of the uterine tubes and the beating of the cilia make the directionality so unlikely that there would need to be an immense anatomic failure to expel the stratum basale out the uterine tubes. In endometriosis, there is usually no anatomical defect.

Another thought is **metastasis**, spread hematogenously or lymphatically. Because the endometrial tissue in endometriosis is **ectopic** (not in the uterus) **but completely normal**, without any evidence of dysplasia, invasion, or genetic alteration, it is highly unlikely that endometriosis is caused by metastasis. Certainly, the ischemic and necrotic stratum functionale will not accidentally metastasize, revert from ischemia, and establish a new epithelium somewhere else. Endometrial cancer doesn't spread through blood and lymphatics. And if an epithelium gained the ability to metastasize, it would continue to do so, causing eruptions of endometriosis after having them removed. Endometriosis doesn't do that.

Neither retrograde flow nor metastatic noncancer is the cause, despite being the leading theories.

A solid theory that we at OME can endorse (although we like the last one best) is that the mesothelial cells that become endometrial tissue aren't ectopic at all but have gone rogue. **Mesothelial metaplasia** could also explain why endometriosis can be found near any viscera—the mesothelial cells of every Body Cavity are the mesothelial cells of the first Body Cavity, the intraembryonic coelom, and the same mesothelial cells of the Müllerian ducts. Wherever there is a Body Cavity, there are mesothelial cells that can theoretically become endometrium. However, if there were metaplasia of mesothelial tissue, there would be evidence of genetic changes, but none are found in endometriomas. Metaplasia should come with some risk of cancer; endometriosis doesn't. And no mesothelioma (cancer of the mesothelium) ever exhibits any evidence of endometrial tissue. As endometriosis isn't found in the limbs, brain, or

spinal cord but *is* found in every compartment that involves a Body Cavity (lungs, pleural cavities; mediastinum, pericardial cavity; abdomen, peritoneal cavity), it could be that the mesothelium got confused as to where it was and became endometrium instead.

The theory we favor is **ectopic progenitor cells**. The uterus and uterine tubes develop from the Müllerian duct. The Müllerian duct is an invagination of the intraembryonic coelom (mesothelial cells) that invaginates lateral to and at the height of the mesonephros. The mesonephros spans the thorax, abdomen, and pelvis of the developing embryo. So, too, do the paramesonephric ducts (the Müllerian ducts). If any of the cells that are destined to become uterus or uterine tubes get left behind ANYWHERE on that track, or if another organ proliferates too quickly and takes with it the cells of that duct, then primordial endometrial tissue (the mesothelial cells of the intraembryonic coelom that are now the Müllerian duct cells) can end up anywhere. That primordial endometrial tissue then does what it is programmed to do—build a stratum basale and proliferate during the proliferative phase, secrete during the secretory phase, and die off in the menstrual phase. These ectopic progenitor cells were supposed to stay part of the Müllerian duct and do Müllerian duct things, they were just misplaced or carried away from the Müllerian duct. This explains how endometriosis can end up in the visceral cavities—chest, abdomen, pelvis—and not in the brain or limbs.

Dr. Williams' Favorite Family Feud Clip (Steve Harvey Era).
https://www.youtube.com/watch?v=fdcleUk-T4U